REMARKS

In the Final Action dated December 8, 2005, Claims 1-10 and 16-17 are pending and under consideration. Claims 11-15 have been cancelled as directed to non-elected subject matter. Applicants reserve the right to file a divisional application to pursue the subject matter of Claims 11-15. Claims 1-10 and 16-17 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 4,676,982 to Hassig ("Hassig"), in view of U.S. Patent No. 4,477,432 to Hardie ("Hardie"), and further in view of Park et al. (*Arthritis and Rheumatism*, vol 37, p. R5, 1994) ("Park et al.") and Ibbotson et al. (*Gut*, vol 36, p. 1-4, 1995) ("Ibbotson et al.").

This Response addresses the Examiner's sole rejection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-10 and 16-17 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hassig, in view of Hardie, and further in view of Park et al. and Ibbotson et al. The Examiner alleges that the primary reference to Hassig teaches a method of treating certain IBD diseases by intravenously administering a pooled human immunoglobulin preparation. The Examiner alleges that the secondary reference to Hardie discloses a method for treating enteric infection by orally administered immunoglobulin; and that oral administration of immunoglobulin has certain advantages over intravenous administration (i.e., to avoid pain from an injection). The Examiner alleges that Park et al. teach the treatment of rheumatoid arthritis (RA) by orally administering pooled human immunoglobulin to neutralize superantigens related to the RA pathogenesis. The Examiner further alleges that Ibbotson et al. suggest that superantigens are involved in the pathogenesis of IBD.

Thus, the Examiner contends that one skilled in the art at the critical time would have been motivated to substitute the "advantageous" oral administration of immunoglobulin taught by Hardie for the intravenous administration of immunoglobulin taught by Hassig. The Examiner contends that considering that Park et al. suggest that pooled human immunoglobulin may neutralize superantigens related to the pathogenesis of RA, and further considering that Ibbotson et al. suggest that superantigens may be involved in the pathogenesis of IBD, one skilled in the art at the critical time would have been motivated to treat IBD with orally administered pooled human immunoglobulin.

Applicants respectfully submit that the Examiner's proposition fails to establish a *prima facie* case of obviousness. At best, the Examiner's proposal establishes only that it would have been "obvious to try" the asserted combination, without a reasonable expectation of success. Notably, the Examiner's analysis employs considerable impermissible hindsight; and the motivation to combine the references is not properly found in the cited art, absent reference to the present invention.

Applicants submit that the present invention, for the first time, surprisingly identifies that oral administration of pooled human immunoglobulin is therapeutically effective for treating IBD.

Applicants emphasize that the etiology of IBD remains unknown. Hence, a combination of prior art that is premised upon a certain alleged "etiology" of IBD is ultimately based on speculation and cannot support an assertion of obviousness. Applicants observe, for example, that the primary reference to Hassig acknowledges, in the first instance, that "[c]ertain inflammatory conditions of the bowel are of unknown etiology and are difficult to treat." Hassig, col. 1, lines 9-10 (emphasis added). Hassig further specifies ulcerative colitis (col. 1,

line 11) and Crohn's disease (col. 1, line 13) as known IBD diseases, which are of "unknown etiology." Although Hassig teaches intravenous administration of immunoglobulin in the treatment of IBD, Applicants respectfully submit, as admitted by the Examiner, that there is, however, no recognition in Hassig, or any other reference cited on this record, that oral administration of pooled human immunoglobulin would be therapeutically effective for treating IBD. Indeed, it is known in the art that immunoglobulin is a special form of protein molecule and thereby can be degraded by digestive system. Thus, contrary to the Examiner's allegation, one skilled in the art in view of Hassig would have not be motivated to employ the Hassig method by replacing intravenous administration of immunoglobulin with oral administration of immunoglobulin. Even assuming, *arguendo*, one skilled in the art was motivated to employ oral administration of immunoglobulin for treating IBD, in the absence of the teaching of the present invention, there would have been simply no reasonable expectation of success based on the scientific knowledge that proteins can be degraded by digestive system.

Notably, the cited secondary references, taken separately or in combination, do not ameliorate the deficiencies of Hassig.

A rejection of claimed subject matter as obvious under 35 U.S.C. §103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed device or composition, or carry out the claimed process; and (2) whether the prior art would have suggested that in so carrying out the claimed process, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). There is no suggestion in the art of record to treat IBD by orally administering pooled human polyclonal immunoglobulin, as

presently claimed. Nor is there any expectation in the prior art on this record that oral administration of pooled human immunoglobulin can in fact treat IBD.

Hardie is directed to the use of orally administered immunoglobulin for treating enteric infections, e.g., infections caused by *E. coli, V. cholera,* or *S. typhosa;* or for treating intoxications, e.g., infantile botulism, (col. 7, lines 3-10 of Hardie). Applicants observe that enteric infections are diseases that, unlike IBD, have known etiologies, e.g., are caused by bacteria or viruses. Hardie does not teach or suggest the treatment of any inflammatory disease, let alone IBD.

Hardie also discloses that intact human immunoglobulin, when administered orally, would not lose its therapeutic efficacy. According to Hardie, the therapeutically effective immunoglobulin is delivered (via oral administration) to the site where the therapeutic activity of the immunoglobulin is required. However, nowhere does Hardie teach or suggest that treating IBD requires the therapeutic activity of immunoglobulin in the gastrointestinal tract. In fact, Hardie discloses that orally administered immunoglobulin "may be used in prevention or treatment of enteric infections . . . since intact IgG with opsonic activity persisted in the gastrointestinal tract and thus is available to function in such prevention or treatment." See, Hardie, col. 7, lines 3-8 (emphasis added).

Applicants submit that it is well known in the art that the opsonic activity of IgG involves guiding phagocytic cells to ingest and destroy the infection-causing bacteria by coating such bacteria with IgG that would be recognized by the phagocytic cells. Thus, Hardie teaches, at most, that if retained intact in the gut, immunoglobulin is useful for treating enteric infection. One may not, however, extrapolate the therapeutic activity of intact immunoglobulin in treating enteric infection to treating all other diseases affecting the gastrointestinal tract.

Moreover, Applicants observe that the intestinal infections in Hardie merely involve immature infants. Applicants submit that the gastrointestinal tract of an infant is physiologically and biochemically distinct from that of an adult or a child, which carries a mature digestive system that may readily degrade immunoglobulin.

Applicants observe that Hardie assumes that to be effective, immunoglobulin molecules must survive the gastrointestinal environment to reach their target areas with intact biological properties. However, there is no teaching or suggestion in Hardie that orally administered immunoglobulin can survive the gastrointestinal environment in adults and children. Accordingly, Applicants respectfully submit that to combine Hassig and Hardie to achieve the present invention, one must assume that immunoglobulin would also survive the gastrointestinal environment in adults and children, which assumption is both unwarranted and unfounded in the references on this record. In fact, Hassig clearly acknowledges that immunoglobulin may be cleaved or degraded by pepsin (a well-known enzyme that exists at high concentration in mature digestive systems). See Hassig, col. 1, lines 32-35. Thus, Hassig teaches away from the present invention or at least suggests avoiding administration of immunoglobulin via oral or other gastrointestinal route. Alternatively, to combine Hassig and Hardie as contended by the Examiner, one has to assume that degraded immunoglobulin can still function for treating IBD. Such assumption is flatly contradicted by the disclosures of Hassig and Hardie, which explicitly require intact immunoglobulin for therapeutic efficacy. Notably, the recognition of the present invention is not premised on the ground that immunoglobulin remains completely intact in the gut in the first place.

Furthermore, even assuming immunoglobulin would have remained intact in the gut of adults and children, one skilled in the art could only guess as to whether or not the intact

immunoglobulinin the gastrointestinal tract could function to treat IBD. Moreover, absent the teachings of the present invention, the result of treating IBD by oral administration of pooled human immunoglobulin would be, at best, unpredictable.

Accordingly, Hardie merely teaches that molecular integrity may be necessary for immunoglobulin 's therapeutic efficacy for treating enteric infections. Hardie does not teach or suggest that oral administration of intact immunoglobulin is either necessary or sufficient for treating IBD.

Thus, Hardie does not ameliorate the deficiencies of Hassig as to whether oral administration of immunoglobulin can be employed to treat IBD.

The reference to Park et al. is a one-paragraph meeting abstract in which certain beneficial effects resulting from the oral administration of immunoglobulin to RA patients in a 6-week study are disclosed. Nowhere do Park et al. disclose or suggest a method for treating IBD. Even to the extent of treating RA, Park et al. admit that the reported results are from a "limited period of observation" and merely "encourage further evaluation" of oral immunoglobulin in the treatment of RA. Park et al. further speculate that the neutralization of superantigens by immunoglobulin may be implicated in the treatment of RA as disclosed, or that such mechanism could explain these initial observations. Careful reading of such disclosure, in the absence of the present invention, however, provides merely an invitation to further experimentation. Park et al. do not remotely suggest, as the Examiner asserts, that RA or any autoimmune disease, particularly a disease of unknown etiology, such as IBD, is in fact caused by superantigens; or could be addressed on that basis.

The Examiner also relies on Ibbotson et al. to support the proposition that IBD is caused by superantigens. Applicants observe that the Ibbotson et al. reference is not a research

article reporting original discoveries, but merely a review article discussing the potential role of superantigens in the pathogenesis of Crohn's disease. (See the title and the paragraphs starting under the last heading on page 2, right column (emphasis added)). Applicants observe that the last two paragraphs of Ibbotson et al., upon which the Examiner relied in the Office Action, merely propose a possible factor among many others allegedly involved in the etiologies of IBD.

In this connection, in the response filed September 23, 3005, Applicants submitted copies of certain references. Applicants submit that the above-mentioned references teach numerous clinical, epidemiological, and experimental studies that have been conducted in an attempt to elucidate the etiology of IBD (for example, Fiocchi, *Gastroenterol.* 1998; 115:182-205, attached as Exhibit A in the response filed September 23, 3005 and Banic et al. *Acta Med Croatica* 1997;51(1):37-40), attached as Exhibit B in the response filed September 23, 3005). Applicants submit that many factors, individually or in combination, have been suggested or suspected as possible causative agents for IBD, e.g., genetic factors (McLeod et al. *Dis Colon Rectum* 1997;40(5):553-7), microbial factors (Stable *J Dáiry Sci* 1998;81(1):283-8), viral factors (Smith and Wakefield *Ann Med* 1993;25(6)557-61), immunological factors (Beil et al. *J Leukoc Biol* 1995;58(3):284-98), nutritional factors (Bielefeldt et al. *Gastroenterol* 1989;27(9):455-8), thrombotic factors (Levine et al. *J Pediatr Gastroenterol Nutr* 1998;26(2):172-4) and environmental factors (Koutroubakis et al. *Hepatogastroenterology* 1996;43(8):381-93) (attached as Exhibits C to I in the response filed September 23, 3005). Applicants respectfully submit that in spite of the many suspected factors or mechanisms, as illustrated above, and the increasing interest in treating IBD, none of the studies has been able to demonstrate a reasonably clear cause and effect relationship and the etiology of IBD remains unknown.

In fact, Ibbotson et al. clearly state that the etiology of IBD "remains unknown" (the first paragraph of the article) and "searches for evidence of autoimmune reactions in IBD, especially Crohn's disease, have been negative" (the first full paragraph on page 3, left column).

Thus, Applicants respectfully submit that in the context of a disorder with still unknown etiology and no viable treatment, the collective wisdom of the art at the relevant time provide no more than an invitation to experiment which satisfies only an "obvious to try" standard, long rejected under the law. *Ex parte Goldgaber*, 41 USPQ 2d 1172, 1177 (B.P.A.I. 1996) (quoting *In re Eli Lilly and Co.*, 902 F.2d 943, 945, 14 USPQ 2d 1741, 1743 (Fed. Cir. 1990)).

Even assuming, *arguendo*, that one skilled in the art was motivated to combine the teachings of Hassig and the secondary references at the time the present application was filed, there would have been no reasonable expectation of success to achieve the present invention. As discussed above, to combine the cited art in the manner the Examiner has asserted, one skilled in the art at the relevant time would have to speculate as to whether immunoglobulin survives adult and children's digestive system; whether immunoglobulin in the gut in fact functions for treating IBD; or whether IBD is in fact caused by superantigens. Based on these speculations, absent the teachings of the present invention, there would have been simply no reasonable expectation of success for one skilled in the art to achieve the present invention, i.e., treating IBD by oral administration of pooled human immunoglobulin.

Furthermore, Applicants respectfully submit U.S. Patent Application Publication No. US 2003/0099635 to Barstow et al. ("Barstow et al.") (copy enclosed as Exhibit 1). Barstow et al. teach a method of treatment for immune-mediated neurodegenerative diseases using alimentary administration, e.g., oral administration, of immunoglobulin. Particularly, Example 2

of Barstow et al. provides remarkable results demonstrating that oral administration of immunoglobulin can prevent or attenuate inflammation in gastrointestinal environment. For example, Example 2 and Table 1 show significant GI severity index score decreases after oral administration of immunoglobulin. See pages 7-8 of Barstow et al. Most notably, Table 1 and Figure 1 of Barstow et al. show that 55% of the patients had remission of GI symptoms and 78% of the patients had improvement of GI signs and symptoms. *Id.* Applicants respectfully submit that the showing of Barstow et al. provides corroborative evidence that supports the unexpected result of oral administration of immunoglobulin recognized by the present invention.

Moreover, there had been an increasing interest and a long-felt need for an effective treatment method for IBD at the time the present invention was filed. See, e.g., the webpage (http://people.hsc.edu/faculty-staff/edwardd/edsweb01, attached as Exhibit J in the response filed September 23, 3005) of Dr. Edward W. Devlin at Hampden-Sydney College, Hampden-Sydney, Virginia and the specification, page 2, line 15 to page 5, line 7.

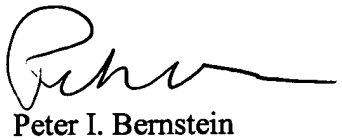
Applicants respectfully submit that the present invention provides a successful solution to this long-standing problem. The hypothetical combination of the cited references is not likely to defeat an invention where the evidence shows that long-standing problems were solved. *Kalman v. Kimberly-Cark Corp.*, 713 F.2d 760, 774, 218 U.S.P.Q. 781, 791 (Fed. Cir. 1995). Long-felt need in the face of prior art later asserted to lead to a solution tends to negate the proposition that the combination of such prior art would have been obvious. *Micro Chem., Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2d, 1238, 1245 (Fed. Cir. 1997) (emphasis added). Thus, by solving a long-standing problem, the present invention is not obvious in view of the cited art.

Furthermore, Applicants submit that the Examiner's combination of Hassig, Hardie, Park et al. and Ibbotson et al. can, in fact, only be made with the benefit of hindsight, derived from the disclosure of the present application. Applicants submit that the rejection of claimed subject matter under 35 U.S.C. §103 requires that both the suggestion to carry out the claimed invention and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991) (emphasis added). Here, the suggestion and the expectation of success of a method for treating IBD by oral administration of pooled human immunoglobulin preparation appears nowhere in the cited art, and only in the present application.

In view of the above remarks, it is respectfully submitted that the present invention is not-obvious in view of Hassig, Hardie, Park et al. and Ibbotson et al. Accordingly, the rejection of Claims 1-10, under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Enclosure: Exhibit 1